REMARKS

Claims 1 and 11 to 16 are present for purposes of prosecution.

Claims 4 to10 have been withdrawn from consideration as being directed to a non-elected invention.

Reconsideration of the rejection of this application is respectfully requested in view of the following remarks.

Applicants' invention as defined in independent Claim 1 is directed to a pharmaceutical composition which is a single dosage formulation in the form of a tablet containing metformin and glipizide which formulation contains 2 to 3% moisture, and including an outer protective coat or finishing layer surrounding the tablet, the formulation being designed to control moisture so that the glipizide does not hydrolyze and the metformin is compressible. Applicants' formulation as claimed is devoid of an enteric coating. It cannot be a sustained or controlled release formulation (as disclosed by the cited Chen et al. patent (discussed hereinafter)) without an enteric coating.

The outer protective coating or finishing layer is not an enteric coating and will not serve to control or sustain release of the metformin and/or glipizide, but only serves to protect the tablet from physical abrasion and prevent contact of the drug with liquids which cause premature dissolution and release of drug before it is ingested or before it is swallowed. The outer protective coating acts as a barrier against moisture and will minimize hydrolysis of the glipizide. See Example 1, page 26, lines 19 to 26 of the Specification.

The Examiner objects to the amendment filed December 13, 2004. The Examiner contends that the amendment introduces new matter in the phrase "being devoid of an enteric coating".

Claims 1 and 11 to 16 are rejected under 35 U.S.C. §112, first paragraph on the grounds that the claims introduce new matter, in that the amendment filed February 23, 2004 introduces new matter in the phrase "being devoid of an enteric coating".

The Examiner contends that:

> "The instant specification discloses that the pharmaceutical compositions of the present invention includes a combination of metformin and glipizide in a single formulation, wherein the glipizide content is uniform, and which formulation controls moisture so that the glipizide does not hydrolyze, yet the metformin is compressable; and wherein the metformin and glipizide are formulate together in a bilayered tablet which includes a first layer and a second layer (page 7, line 18 thru page 8, line 16).

> The specification states that the bilayered tablet of the invention may include an outer protective coating or finishing layer. As the specific embodiments of the outer protective coating or finishing layer of the tablet, the enteric coating is illustrated throughout the specification (page 8, lines 32-36; page 9, lines 1-18; page 16, line 1 thru page 17, 12)."
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> "The instantly recited 'said composition being devoid of an enteric coating' completely excludes any possibility of having 'enteric coating' on the outer surface of the single dosage formulation (e.g., tablet). There is no support in the specification for such negative limitation made by the present claimed invention."

It is submitted that Applicants' Specification clearly provides support for use of the phrase "said composition being devoid of an enteric coating".

At page 12 of the Specification, starting at line 15, it is indicated that "tablets of the invention may also include a coating layer which may comprise 0 to about 15% by weight of the tablet composition. The coating may comprise any conventional coating formulations . . . ."

Conventional coating formulations may include enteric coating or sustained release formulations. However, Applicants indicate at page 12, lines 1 and 2, that the coating layer may comprise 0% by weight of the tablet composition meaning that there is no enteric or sustained release layer.

In addition, at page 17, lines 13 to 15, it is stated that:

> "In still a further embodiment, neither the glipizide particles nor the metformin particles need to be enteric coated."

IN THIS EMBODIMENT, IT IS CLEAR THAT AN ENTERIC COATING IS NOT PRESENT, BUT IT IS LEFT OPEN FOR AN OUTER PROTECTIVE LAYER TO BE PRESENT.

At page 19 starting at line 26 of the Specification, it is indicated that:

> "The tablets thus obtained may then optionally be coated with a hydrophilic cellulose polymer and talc."

The key word is "optionally" meaning that the Applicants' tablets need not be coated with such polymer.

Thus, Applicants' disclosure clearly supports use of the phrase "being devoid of an enteric coating".

The fact that Applicants disclose that it is possible to employ (or not to employ) enteric coated particles of glipizide and/or metformin is immaterial. This is Applicants' own disclosure and

it cannot be used against Applicants as the Examiner is attempting to do. In re Ruff et al., 118 USPQ 340 (CCPA 1958).

In view of the foregoing, it is submitted that Claims1 and 11 to 16 are in compliance with 35 U.S.C. §112, first paragraph.

Claims 1 and 11 to 16 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chen et al. (U.S. 6,099,862) in view of Patel et al. (U.S. 6,248,363 B1) and Bonhomme et al. (U.S. Patent No. 6,303,146).

The Examiner contends that:

> "Chen teaches a pharmaceutical tablet containing [a] combination of metformin and glipizide, wherein core of said composition is prepared by mixing metformin and glipizide with povidone, sodium lauryl sulfate and magnesium stearate and then tablet is optionally seal coated with an opadry materals. As specific embodiments of the claimed invention, Examples (1-2) discloses 850mg or 500mg of metformin HCI and 5 mg of glipizide controlled release tablet, wherein granules containing metformin and glipizide are dried 'in the fluidized bed coater until the loss on drying is less than 2%' and then compressed to tablet."
>
> "Patel is being supplied as a reference to demonstrate the routine knowledge in art in preparing pharmaceutical actives such as metformin and glipizide in various pharmaceutical delivery systems including various dosage forms (e.g., tablet, capsule, quick or fast dissolving tablet, granule, etc...); coated with various coating methods (e.g., enteric coating, seal coating, protected coating or layered coating, etc...); and dosage form release system (e.g., immediate release pulsatile release, controlled release, extended release, delayed release, targeted release). See column 6, line 32; column 7, line 7; column 9, line 33 and 66; column 10, line 31; column 41, line 29 thru column 51, line 10."
>
> "Bonhomme is being supplied as a reference to demonstrate the routine knowledge in the art in determining 2-3% w/w moisture content prior to 'tableting' (column 6, lines 37-49)."
>
> "The teaching of Chen differs from the claimed invention in 'being devoid of an enteric coating'; '2 to 3% by weight moisture'; and the specific dosage amounts of metformin and glipizide in said composition. However, it would have been obvious in view of Patel (US 6248363 B1) who teaches pharmaceutical delivery systems for pharmaceutical active ingredients including metformin and glipizide, wherein said active ingredients can be prepared in various dosage forms (e.g., tablet, capsule, quick or fast dissolving tablet, granule, etc...); coated with various coating methods (e.g., enteric coating, seal coating, protected coating or layered coating, etc...); and dosage form release system (e.g., immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release), and Bonhomme who teaches the

routine knowledge in art in determining 2-3% w/w moisture content prior to 'tableting'.

"The above references in combination make clear that the combination of metformin and glipizide in single dosage formulation is old and well known in the art. The above references in combination also make clear that the preparation of pharmaceutical composition containing metformin and/or glipizide in various dosage forms (e.g., tablet, quick, fast dissolving tablet, capsule, etc...) coated with coating techniques (e.g., enteric coating, protective coating, seal coating, etc...) designed for various dosage form release systems (e.g., immediate release, controlled release, delayed release, etc...) is old and well known in the art. Furthermore, the above references in combination make clear that optimization of 'less than 2%' to '2 to 3% moisture' is well within the skill of the artisan. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a)."

"With respect to the instantly required 'devoid of an enteric coating', Patel teaches that determination of appropriate dosage forms (e.g., tablet covered with enteric coating or with protective coating or finishing layer) having optimum therapeutic index is well considered within the skill of the artisan, ant the artisan would be motivated to determine optimum dosage forms to maximize the effects of the drug. Therefore, the references in combination make obvious the claimed invention."

"With respect to the specific dosage amounts of active ingredients in said composition, those of ordinary skill in the art readily optimize effective dosages as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information in column 5, lines 1-15."

It is submitted that Applicants' invention claimed in Claims 1 and 11 to 16 is patentable over Chen et al.

Chen et al. disclose a controlled release tablet which, as disclosed in Example 1, may include a combination of metformin HCl (800 mg) and glipizide (5 mg) in a tablet core and as disclosed in Example 2, may include a combination of metformin HCl (500 mg) and glipizide (5 mg) in a tablet core. The Chen et al. Examples 1 and 2 tablet cores include a seal coating and a sustained release

coating formed of a semi-permeable membrane which as will be seen is an enteric coat which will prevent release of drug prior to reaching the intestines. The sustained release coating includes one hole drilled onto each side of the sustained release tablet, which holes allow for release of drugs into the intestines. As indicated in Examples 1 and 2 (Col. 7, lines 4-5 and Col. 8, lines 25 to 26) of Chen et al., the Chen et al. tablet is tested in simulated intestinal fluid which indicates that the tablet is expected to release drug in the intestines and not the stomach. This means that the Chen et al. semi-permeable membrane is an enteric coat.

As indicated in Column 3, lines 61 to 64 of Chen et al.,

> "The semipermeable membrane is permeable to the passage of an external fluid such as water . . ."

Applicants' tablet as claimed must contain at least 2% moisture so that it is compressable but no more than 3% moisture so that the glipizide will not hydrolyze. Such a semi-permeable will not control moisture as required by Applicants' Claim 1. Applicants use the outer protective coating to control moisture content.

Applicants' tablets include an outer protective layer to prevent moisture from seeping into the table and not a semi-permeable membrane permeable to water (Col. 3, lines 61 to 63, Chen et al.). The Chen et al. semi-permeable membrane is actually an enteric coating as seen by the fact that the Chen et al. tablet is tested in simulated intestinal fluid (Col. 7, lines 4-5, Col. 8, lines 25 to 33) and not in stomach acid. An enteric coat prevents release of drug prior to reaching the intestines.

The tablet cores of Examples 1 and 2 of Chen et al. are formed by a granulation technique where granules containing metformin and glipizide "are dried in the fluidized bed coater until the loss on drying is less than 2%."

It is submitted that Applicants' composition as claimed in Claims 1 and 11 to 16 are patentable over Chen et al. As indicated, in Claim 1, Applicants' tablets are devoid of an enteric coating. The Chen et al. tablets contain a sustained release layer which is a semi-permeable membrane and thus are sustained release tablets, which as shown in Examples 1 and 2 release drugs over a 16 hour period. In fact, if Applicants employed a semi-permeable membrane as in Chen et al., instead of an outer protective coating, it could conceivably cause Applicants' tablet to dry to less than 2% moisture or to absorb moisture to greater than 3%. This would defeat the purpose of

Applicants' invention as defined in Claim 1. Applicants employ the outer protective coat and not a semi-permeable membrane as in Chen et al.

Applicants' tablets must include sufficient moisture (2 to 3%) to leave the metformin sufficiently compressible so that tablets may be formed. However, the water content must not be greater than 3% to ensure that the glipizide will not be hydrolyzed.

There is no disclosure or suggestion in Chen et al. of a tablet which is devoid of an enteric coat and that contains 2 to 3% moisture.

There is nothing in Chen et al. which would motivate one skilled in the art to change the Chen et al. tablet (originally designed as a sustained release tablet with a semi-permeable membrane (permeable to water) which includes openings in the tablet to allow drugs to be released) to form a tablet which is devoid of an enteric coating and must contain 2-3% moisture.

The differences between Applicants' invention as claimed and the tablet of Chen et al. are significant and unobvious so that the subject matter of Applicants' invention as a whole would not be obvious to one skilled in the art.

For the aforementioned reasons, it is submitted that Applicants' invention as claimed in Claims 1 and 11 to 16 is patentable over Chen et al.

It is submitted that Applicants' invention as claimed in Claims 1 and 11 to 16 is patentable over U.S. Patent No. 6,248,363 to Patel et al.

Patel et al. disclose solid pharmaceutical compositions which include a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate, the encapsulation coat including at least one ionic or non-ionic hydrophilic surfactant and/or a lipophilic surfactant or a triglyceride, and a pharmaceutical active component. Other similar embodiments are disclosed as well, all of which much include an encapsulation coat which will contain the pharmaceutical active ingredient.

There is no disclosure or suggestion in Patel et al. of a tablet which includes a combination of metformin and glipizide. In addition, there is no disclosure or suggestion in Patel et al. of a tablet which must be prepared in a manner to include 2 to 3% moisture to leave the metformin sufficiently compressible so that tablets may be formed while ensuring that the water content is not greater than 3% so that the glipizide (employed in combination with the metformin) will not hydrolyze.

Furthermore, Patel et al. include their pharmaceutical active ingredient in the encapsulation coat while Applicants employ the metformin and glipizide in the tablet core.

For the above reasons, it is clear that Applicants' composition as claimed is patentable over Patel et al.

U.S. Patent No. 6,303,146 to Bonhomme et al. relates to a solid oral dosage form containing a combination of metformin and glibenclamide, and not glipizide as is required in Applicants' formulation.

The Examiner refers to Col. 6, lines 37-49 of Bonhomme "to demonstrate routine knowledge in the art in determining 2-3% w/w moisture content prior to 'tableting'."

Bonhomme et al. teach that there was a loss of 2-3% w/w on drying. However, there is no disclosure or suggestion of a tablet containing metformin and glipizide containing 2-3% by weight moisture. Accordingly, Bonhomme et al. has nothing whatsoever to do with Applicants' invention.

It is also submitted that Applicants' invention as claimed is patentable over a combination of Chen et al. taken with Patel et al. and Bonhomme et al.

Chen et al. teaches a sustained release tablet which contains a combination of metformin and glipizide in a tablet core which is coated with a seal coating and a sustained release coating which is an enteric coating since it releases drug in the intestines (this cannot be present in Applicants' tablet). Applicants' composition includes the outer protective coating but does not include the Chen et al. sustained release coating (which is an enteric coating). The Chen et al. tablets include less than 2% moisture whereas Applicants' composition must include at least 2% moisture but no more than 3% moisture. Thus, Chen et al. is totally devoid of Applicants' inventive concept as defined in Claim 1, that is a pharmaceutical composition which does not include an enteric or sustained release coating and which includes from 2 to 3% moisture which allows the metformin to be compressible to enable tablet formation but which will not cause hydrolysis of the glipizide. The above differences are material and unobvious. Patel et al. adds nothing to Chen et al. which would make Applicants' composition obvious. Patel et al. does not disclose a pharmaceutical composition containing a combination of metformin and glipizide. Patel et al. does not address the moisture problem employing metformin and glipizide in a single formulation and its solution. Patel et al. disclose employing an encapsulation coat which will contain the active component whereas Applicants employ the metformin and glipizide in the tablet core. Bonhomme just teaches drying a combination

of metformin and glibenclamide wherein 2-3% w/w moisture is eliminated and not left in the composition. A combination of Chen et al. and Patel et al. would merely suggest to or motivate one skilled in the art to include a drug in the enteric coating of Chen et al. and do nothing about moisture content. Bonhomme et al. suggests losing 2-3% moisture. At best the rejection of the claims is based on modifying the Chen et al. enteric coated sustained release tablet, using hindsight in view of Applicants' disclosure, so as to completely change its basic nature to omit the sustained release or enteric coating. The latter would, of course, be improper as lacking any foundation, in fact. There is nothing in either Chen et al., Patel et al. and/or Bonhomme et al. that would suggest that Chen et al. should be so modified. Thus, it is submitted that Applicants' invention as claimed is patentable over the combination of Chen et al. taken in view of Patel et al. and Bonhomme et al.

Absent the use of hindsight in view of Applicants' disclosure, there would be no reason for one skilled in the art reading the cited references to combine these references. The use of hindsight in view of Applicants' disclosure in combining references to reject Applicants' claims is clearly improper in view of In re Pye et al., 148 U.S.P.Q. 426 (CCPA 1966), ACS Hospital Systems, Inc. v. Montefiore Hospital, supra.; and W.L. Gore & Assoc., Inc. v. Garlock, Inc., supra.

In the "Response to Arguments" on page 8 of the Official Action, the Examiner maintains that:

> "Applicant's argument takes position that applicant's tablets are devoid of an enteric coating and therefore are immediate release tablets. Applicant alleges that the Chen's sustained release tablets differ from the instantly claimed immediate release tablets."
>
> "Unlike applicant's assertion, there is no indication in the present claims, however that said composition must be in the form of immediate release tablets. Applicant's recitation of 'being devoid of an enteric coating' does not render the claimed composition to be essentially in the form of immediate release tablet. Since the interpretation of 'being devoid of an enteric coating' means other types of known coating techniques of pharmaceutical compositions (e.g., seal coating, film coatings, barrier coatings, compress coatings, fast disintegrating coatings, or enzyme degradable coatings) designed for diverse dosage delivery forms, for example immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release, synchronized release, or targeted delayed release (see column 41, lines 55-63 of US 6248363), Chen's formulation makes obvious the claimed invention."

The proviso "said composition being devoid of an enteric coating" excludes any possibility of having an "enteric coating". In addition, Applicants' tablet as claimed cannot include a semi-permeable membrane permeable to water since Applicants must control moisture content.

The "outer protective coating or finishing layer surrounding said tablet" defined in Claim 1 is not an enteric coating or a semi-permeable membrane as used by Chen et al. and does not encompass an enteric coating or a semi-permeable membrane. Claim 1 defines the composition as being devoid of an enteric coating. Thus, the outer protective coating or finishing layer must be other than an enteric coating. In addition, Applicants' tablet must contain 2-3% moisture. The Chen et al. semi-permeable membrane allows water to penetrate the membrane and therefore would not be designed to control moisture as required in Applicants' Claim 1. The term "enteric coat" generally refers to preventing a tablet from releasing drug not in the stomach but in the intestines.

In fact, the Chen et al. semi-permeable membrane is an enteric coating. As seen in Column 7, lines 4-5 and Column 8, lines 25 to 53, it is indicated that the Chen et al. tablet is tested in simulated intestinal fluid. This indicates that the Chen et al. tablet will pass from the stomach into the intestines where the drug is released. Thus, the semi-permeable membrane acts as an enteric coating. If the Chen et al. semi-permeable membrane were not an enteric coating, the Chen et al. tablet would have been tested in stomach acid for drug release properties and not in simulated intestinal fluid.

In Applicants' Specification at page 9, lines 1 to 5 and at page 16, starting at line 25, "enteric coated glipizide particles" are disclosed. It is also indicated that the enteric coated glipizide particles "may be further coated with an outer protective finishing coat or layer . . . ." Applicants would not coat enteric coated particles with an enteric coating or a semi-permeable membrane. The protective finishing coat or layer is exactly that, a protective coat and not an enteric coat. Applicants' protective finishing coat or layer protects the composition from physical abrasion or premature contact with liquids or other materials which could possibly cause premature release of the drug. The protective finishing coating or layer functions to delay release of the drug before the dosage form is ingested or swallowed. Once swallowed, the protective coat does not delay or control release of drug in the body.

Protective finishing coat or layer is not encompassed by "enteric coat" which delays or controls release of drug.

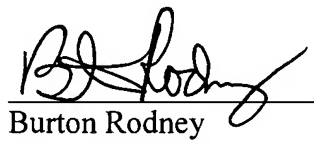
The Examiner further states that:

> "Applicant's argument takes position that there is no disclosure or suggestion in Chen et al. of '2 to 3% moisture' of tablet. The examiner agrees. Chen discloses that the granules containing metformin and glipizide are 'dried in the fluidized bed coater until the loss on drying is less than 2%' prior to 'tableting'. Although Chen's formulation containing 'less than 2%' of moisture differs from the instantly required concentration of '2 to 3% moisture', the examiner considers that such determination is well within the skill of the artisan as evidenced by Bonhomme."

But as indicated thereinbefore, Bonhomme does not teach or suggest a tablet or other dosage form containing 2-3% w/w moisture. This is Applicant's inventive concept for metformin and glipizide combinations and it is not disclosed or suggested in any of the cited references taken alone or in combination.

In view of the foregoing, it is believed that Claims 1 and 11 to 16 overcome all formal objections and are patentable over the cited combination of references. Accordingly, it is believed that Claims 1 and 11 to 16 are in condition for allowance.

Respectfully submitted,



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